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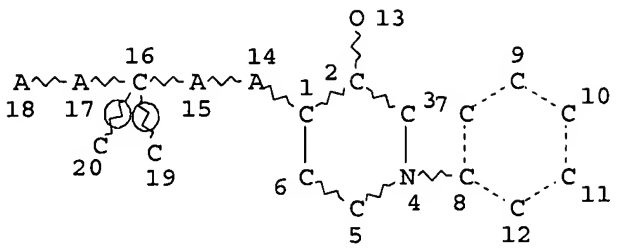

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STEREO ATTRIBUTES: NONE

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100.0% PROCESSED 6262 ITERATIONS 235 ANSWERS
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L4 235 SEA SSS FUL L2

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	173.90	174.11

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=> s l4
L5 2 L4

=> d bib abs 1-2

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:777620 CAPLUS
DN 145:348526
TI An orally active cathepsin K inhibitor, furan-2-carboxylic acid, 1-{1-[4-fluoro-2-(2-oxo-pyrrolidin-1-yl)-phenyl]-3-oxo-piperidin-4-ylcarbamoyl}-cyclohexyl-amide (OST-4077), inhibits osteoclast activity in vitro and bone loss in ovariectomized rats
AU Kim, M. K.; Kim, H. D.; Park, J. H.; Lim, J. I.; Yang, J. S.; Kwak, W. Y.; Sung, S. Y.; Kim, H. J.; Kim, S. H.; Lee, C. H.; Shim, J. Y.; Bae, M. H.; Shin, Y. A.; Huh, Y.; Han, T. D.; Chong, W.; Choi, H.; Ahn, B. N.; Yang, S. O.; Son, M. H.
CS Dong-A Research Laboratories, Dong-A Pharmaceutical Co., Ltd., Gyeonggi-do, S. Korea
SO Journal of Pharmacology and Experimental Therapeutics (2006), 318(2), 555-562
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Human cathepsin K, a cysteine proteinase of the papain family, has been recognized as a potential drug target for the treatment of osteoporosis. The predominant expression of cathepsin K in osteoclasts has rendered the enzyme into a major target for the development of novel antiresorptive drugs. Now, we report the pharmacol. properties of OST-4077 [furan-2-carboxylic acid (1-{1-[4-fluoro-2-(2-oxo-pyrrolidin-1-yl)-phenyl]-3-oxo-piperidin-4-ylcarbamoyl}-cyclohexyl)-amide] as a novel selective cathepsin K inhibitor. Human and rat cathepsin K were inhibited in vitro by OST-4077 with the IC50 values of 11 and 427 nM, resp. OST-4077 suppressed bone resorption induced by rabbit osteoclasts (IC50, 37 nM) but did not affect bone mineralization or cellular alkaline phosphatase activity in MC3T3-E1 cells. Parathyroid hormone-induced bone resorption was inhibited in a dose-dependent manner in thyroparathyroidectomized rats gavaged with a single dose of OST-4077 (ED50, 69 mg/kg). When given orally twice daily for 4 wk to 3-mo-old ovariectomized (OVX) rats, OST-4077 dose-dependently prevented bone loss, as monitored by bone densitometry, ash content, and urinary excretion of deoxypyridinoline. No change in serum osteocalcin in the OVX rats by OST-4077 suggested that bone formation might not be affected by the agent. In summary, OST-4077 selectively inhibited bone resorbing activities of osteoclasts and prevented bone loss induced by estrogen deficiency but did not affect bone formation. OST-4077, an orally active selective human cathepsin K inhibitor, may have the therapeutic potential for the treatment of diseases characterized by excessive bone loss including osteoporosis.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:101158 CAPLUS
DN 140:146014
TI Preparation of 4-[[(1-acylaminocyclohexyl)carbonyl]amino]-1-phenylpiperidin-3-ones as cysteine protease inhibitors and processes for their preparation
IN Lee, Jong-Wook; Lee, Bong-Yong; Lee, Chun-Ho; Hur, Yun; Han, Tae-Dong; Ko, Hyun-Kyoung; Yun, Suk-Won; Shim, Jae-Young; Lim, Joong-In; Son, Moon-Ho; Yang, Jae-Sung; Kim, Mi-Kyung
PA Yuhan Corporation, S. Korea; Dong-A Pharmaceutical Co., Ltd.
SO PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004011457	A1	20040205	WO 2003-KR1502	20030726
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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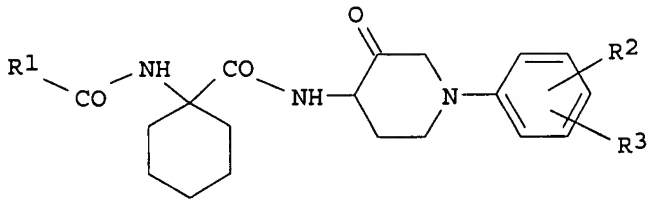
	KR 2004010407	A	20040131	KR 2003-51574	20030725
	AU 2003281698	A1	20040216	AU 2003-281698	20030726
	US 2005234057	A1	20051020	US 2005-521752	20050119
PRAI	KR 2002-44164	A	20020726		
	KR 2003-13889	A	20030306		
	WO 2003-KR1502	W	20030726		

OS MARPAT 140:146014

GI



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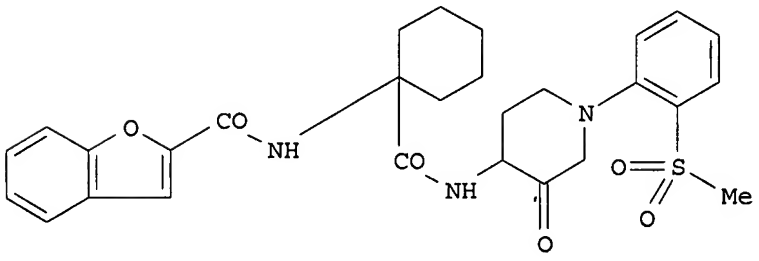

II

AB The present invention provides 1-phenylpiperidin-3-ones (shown as I; variables defined below; e.g. II) and pharmaceutically acceptable salts thereof, having cysteine protease inhibitory activity, pharmaceutical compns. containing the same as an active ingredient, and processes for the preparation thereof. For I: R1 is C1-6 alkyl (un)substituted with Ph, C1-6 alkoxy, or benzyloxy; C2-6 alkenyl (un)substituted with phenyl; C3-6 cycloalkyl; C1-5 alkoxy; Ph substituted with halogen, Ph, trifluoromethoxy, oxopyrrolidyl, mono- or di- C1-4 alkylamino or R4-C1-4-alkoxy (R4 is morpholine, pyrrolidine or piperidine); furanyl (un)substituted with ≥1 functional groups C1-6 alkyl, halogen, and oxopyrrolidyl; benzofuranyl (un)substituted with C1-6 alkyl or R4-C1-4 alkoxy; thiophenyl substituted with C1-6 alkyl or halogen; C1-6 alkylisoxazolyl; pyridyl (un)substituted with halogen; morpholinyl; benzothiophenyl; quinolinyl; pyrazinyl; benzyloxy; oxopyranyl; C1-6 alkyl-7H-imidazo[2,1-b]oxazolyl; C1-6 alkylchromon-2-yl; or (N-tert-butoxycarbonyl)piperidinyl. R2 and R3 are H; hydroxy; nitro; halogen; cyano; C1-6 alkyl (un)substituted with ≥1 halogen atoms; C1-5 alkoxy; C1-5 alkylthio; furyl; 1H-tetrazol-5-yl; oxazolyl; -C(O)R4;

-S(O)nR6, -NR7R8 (R5 is H; hydroxy; C1-6 alkyl; C1-5 alkoxy; mono- or di-C1-6 alkylamino; or C3-6 cycloalkylamino; R6 is C1-6 alkyl; Ph (un)substituted with C1-4 alkoxy; benzyl (un)substituted with C1-4 alkoxy; R7 and R8 are H; C1-6 alkylcarbonyl (un)substituted with halogen, C1-4 alkoxy, or phenyl; C2-6 alkenylcarbonyl; C1-4 alkoxycarbonyl; C3-6 cycloalkylcarbonyl; benzoyl (un)substituted with ≥1 halogen atoms; mono- or di- C1-4 alkylcarbamoyl; or C1-4 alkylsulfonyl, or bonded each ether to form a morpholine, azetidin-2-one, 3,3-dimethylazetidin-2-one, pyrrolidin-2-one, pyrrole, 2,5-dihydropyrrole, piperidin-2-one, oxazolidin-2-one, imidazolidin-2-one, imidazolidin-2,5-dione, tetrazole, 1,1-dioxoisothiazolidine, or C1-6 alkylaziridin-2-one ring; and n = 0-2). Methods of preparation are claimed and .apprx.190 example prepns. are included. For example, II was prepared in 4 steps starting with amide formation from tert-Bu 4-amino-3-hydroxypiperidine-1-carboxylate and 1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexanecarboxylic acid to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-1-(tert-butoxycarbonyl)-3-piperidinol followed by N-deprotection to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-3-piperidinol hydrochloride, followed by N-arylation with 2-fluorophenyl Me sulfone in the presence of K2CO3 to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-1-(2-methylsulfonylphenyl)piperidin-3-ol, followed by oxidation by pyridine-SO3 complex to give II. In some other N-arylations, in addition to the presence of a base, a Pd complex was used as catalyst. IC50 values for inhibition of cathepsin K activity and selectivity for cathepsin K vs. other cathepsins (C, G, H, L, S) are tabulated for many examples of I; e.g. 8.17 nM for II for cathepsin K (382, >240, >240, 138, and 133 nM, resp., for others). The bioavailabilities of I by oral administrations, which were calculated after i.v. administrations of 10 mg/kg of rat, were .apprx.30-90 %.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
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